FROMMER LAWRENCE & HAUG LLP

745 FIFTH AVENUE NEW YORK, NEW YORK 10151

TEL: (212) 588-0800 FAX: (212) 588-0500

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BY FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

The undersigned hereby submits this Citizen Petition, in quadruplicate, pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(j), and FDA regulations 21 C.F.R. §§ 10.30, 314.94, 314.101 and 320.21.

A. Action Requested

That the Office of Generic Drugs of the Federal Food and Drug Administration ("FDA") refuse to accept for filing any Abbreviated New Drug Application (ANDA) for the combination drug amlodipine besylate-benazepril hydrochloride ("amlodipine-benazepril"), unless such ANDA contains both fed and fasted segments of a study demonstrating the bioequivalence of the generic amlodipine-benazepril drug product that is the subject of the application to the reference listed drug LOTREL®.

B. Statement of Grounds

1. Bioequivalence Study Requirements

An ANDA is required to contain "information to show that the new [generic] drug is bioequivalent to the listed drug ..." 21 U.S.C. § 355(j)(2)(A)(iv); 21 C.F.R. §§ 314.(a)(7), 320.21(b). A generic drug product submitted in an ANDA is considered to be bioequivalent to a listed (reference brand-name) drug product if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." 21 U.S.C. § 355(j)(8)(B)(i); 21 C.F.R. § 320.1(e).

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CALIFORNIA OFFICE
4660 LA JOLLA VILLAGE DR. SUITE 850 SAN DIEGO, CA 92122
TEL: (858) 731-5000 FAX: (858) 731-5001

FDA requires that bioequivalence studies for all orally-administered immediate release drug products be conducted under both fed and fasting conditions. A study of the drug taken with food is necessary to determine if there is a food effect that could adversely affect the bioequivalence of the generic drug product to the reference listed drug product. The only exceptions where a fed condition bioequivalence study is permitted to be excluded are: (i) when the test drug and reference drug are both rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and permeability (a BCS Class 1 drug substance); (ii) when the labeling of the reference drug recommends administration on an empty stomach; or (iii) when the labeling of the reference drug makes no statements about the effect of food on absorption or administration. See *FDA Guidance for Industry: Food-Effect Bioavailability and Bioequivalence Studies*, Dec. 2002, at 3.

FDA is required to receive an ANDA (*i.e.*, accept an ANDA for filing) only when it is sufficiently complete for as substantive review, *i.e.*, on its face it contains all data and information required in such an application, including all required bioequivalence data. 21 C.F.R. §§ 314.101 (a)(1), (d)(3).

2. ANDAs for Amlodipine–Benazepril Require Both Fed and Fasting Segments of a Bioequivalence Study

ANDAs seeking regulatory approval of the combination drug amlodipine–benazepril capsules, a prescription drug indicated for the treatment of hypertension, in strengths of 2.5mg/10mg, 5mg/10mg and 5mg/20mg, are eligible for submission to FDA. The reference listed drug is LOTREL®, manufactured by Novartis Pharmaceuticals Corporation.

Under the principles summarized above, each ANDA for a generic amlodipine–benazepril formulation must contain the results of a bioequivalence study purporting to establish that the generic amlodipine-benazepril product is bioequivalent to LOTREL® under both fed conditions (i.e., taken with food) as well as fasting conditions (taken without food).

None of the three exceptions to the fed bioequivalence study requirement applies here. Benazepril is not a BCS Class 1 drug substance, the labeling of LOTREL® does not recommend administration on an empty stomach, and the LOTREL® labeling contains a statement that absorption of the individual active drug substances is not influenced by the presence of food in the gastrointestinal tract. (A copy of the approved LOTREL® package insert is enclosed).

Accordingly, unless an ANDA for a generic amlodipine-benazepril drug product contains a study assessing bioequivalence to LOTREL® under both fed and fasting conditions, the ANDA **should not be accepted for filing** and substantive review, because it is not a sufficiently complete ANDA. 21 C.F.R. § 314.101(a)(1), (d)(3). Thus, FDA is urged to reject for filing any ANDA for amlodipine–benazepril that does not on its face include the results of a study seeking to demonstrate that the generic amlodipine–benazepril drug product is bioequivalent to the reference listed drug product LOTREL® under a fasting condition **and when both are taken with food.**

C. Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of this Citizen Petition.

E. Certification

The undersigned certifies that, to their best knowledge and belief, this Citizen Petition includes all representative data and information known to Petitioner which are unfavorable to the Petition.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP

By: _____
Charles J. Raubicheck

cc: Gary J. Buehler, R.Ph. (HFD-600)
Dale P. Conner, Pharm.D. (HFD-650)
Wm. Peter Rickman (HFD-610)

Lotrel®

C97-30 (Rev. 3/98)

amlodipine and benazepril hydrochloride
Combination Capsules

2.5 mg/10 mg
5 mg/10 mg
5 mg/20 mg

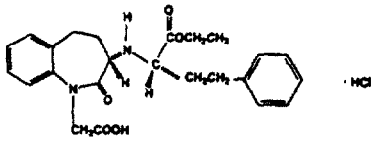
Caution: Federal law prohibits dispensing without prescription.

Prescribing Information

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Lotrel should be discontinued as soon as possible. See Warnings, *Fetal/Neonatal Morbidity and Mortality.*

DESCRIPTION

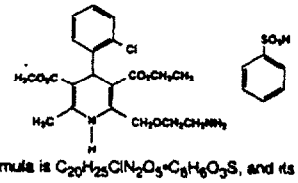
Benazepril hydrochloride is a white to off-white crystalline powder, soluble (>100 mg/mL) in water, in ethanol, and in methanol. Benazepril hydrochloride's chemical name is 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3S)-benzazepine-1-acetic acid monohydrochloride; its structural formula is



Its empirical formula is $C_{24}H_{28}N_2O_5$•HCl, and its molecular weight is 460.96.

Benazeprilat, the active metabolite of benazepril, is a nonsulfhydryl angiotensin-converting enzyme (ACE) inhibitor. Benazepril is converted to benazeprilat by hepatic cleavage of the ester group.

Amlodipine besylate is a white crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Its chemical name is (*R,S*) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulfonate; its structural formula is



Its empirical formula is $C_{20}H_{25}ClN_2O_5$•$C_6H_6O_3S$, and its molecular weight is 567.1.

Amlodipine besylate is the besylate salt of amlodipine, a dihydropyridine calcium channel blocker.

Lotrel is a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated for oral administration with a combination of amlodipine besylate equivalent to 2.5 mg or 5 mg of amlodipine and 10 mg or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate, starch, talc, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex.

Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with benazepril and amlodipine for up to 56 weeks had elevations of serum potassium up to 0.2 mEq/L (see PRECAUTIONS).

Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

ACE is identical to kininase, an enzyme that degrades bradykinin. Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of Lotrel remains to be elucidated.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension.

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Pharmacokinetics and Metabolism

The rate and extent of absorption of benazepril and amlodipine from Lotrel are not significantly different, respectively, from the rate and extent of absorption of benazepril and amlodipine from individual tablet formulations. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract; food effects on absorption from Lotrel have not been studied.

Following oral administration of Lotrel, peak plasma concentrations of benazepril are reached in 0.5-2 hours. Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat, which reaches peak plasma concentrations in 1.5-4 hours. The extent of absorption of benazepril is at least 37%.

Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of Lotrel; the extent of absorption is 64%-90%.

The apparent volumes of distribution of amlodipine and benazeprilat are about 21 L/kg and 0.7 L/kg, respectively. Approximately 93% of circulating amlodipine is bound to plasma proteins, and the bound fraction of benazeprilat is slightly higher. On the basis of in vitro studies, benazeprilat's degree of protein binding should be unaffected by age, by hepatic dysfunction, or—over the therapeutic concentration range—by concentration.

Benazeprilat has much greater ACE-inhibitory activity than benazepril, and the metabolism of benazepril to benazeprilat is almost complete. Only trace amounts of an administered dose of benazepril can be recovered unchanged in the urine; about 20% of the dose is excreted as benazeprilat, 8% as benazeprilat glucuronide, and 4% as benazepril glucuronide.

Amlodipine is extensively metabolized in the liver, with 10% of the parent compound and 60% of the metabolites excreted in the urine. In patients with hepatic dysfunction, decreased clearance of amlodipine may increase the area-under-the-plasma-concentration curve by 40%-60%, and dosage reduction may be required (see DOSAGE AND ADMINISTRATION). In patients with renal impairment, the pharmacokinetics of amlodipine are essentially unaffected.

Benazeprilat's effective elimination half-life is 10-11 hours, while that of amlodipine is about 2 days, so steady-state levels of the two components are achieved after about a week of once-daily dosing. The clearance of benazeprilat from the plasma is primarily renal, but biliary excretion accounts for 11%-12% of benazepril elimination in normal subjects. In patients with severe renal insufficiency (creatinine clearance less than 30 mL/min), peak benazeprilat levels and the time to steady state may be increased (see DOSAGE AND ADMINISTRATION). In patients with hepatic impairment, on the other hand, the pharmacokinetics of benazeprilat are essentially unaffected.

Although the pharmacokinetics of benazepril and benazeprilat are unaffected by age, clearance of amlodipine is decreased in the elderly, with resulting increases of 35%-70% in peak plasma levels, elimination half-life, and area-under-the-plasma-concentration curve. Dose adjustment may be required.

Pharmacodynamics

Single and multiple doses of 10 mg or more of benazepril cause inhibition of plasma ACE activity by at least 80%-90% for at least 24 hours after dosing. For up to 4 hours after a 10-mg dose, pressor responses to exogenous angiotensin I were inhibited by 80%-90%.

Administration of benazepril to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see Warnings, Hypotension).

The antihypertensive effects of benazepril were not appreciably different in patients receiving high- or low-sodium diets.

In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pres-

sure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when coadministered with beta blockers to humans

Amlodipine does not change sinoatrial (SA) nodal function or atrioventricular (AV) conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Over 700 patients received Lotrel once daily in five double-blind, placebo-controlled studies. Lotrel lowered blood pressure within 1 hour, with peak reductions achieved 2-8 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours.

Once-daily doses of benazepril/amlodipine using benazepril doses of 10-20 mg and amlodipine doses of 2.5-5 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10-25/6-13 mmHg.

Combination therapy was effective in blacks and nonblacks. Both components contributed to the antihypertensive efficacy in nonblacks, but virtually all of the antihypertensive effect in blacks could be attributed to the amlodipine component. Among nonblack patients in placebo-controlled trials comparing Lotrel to the individual components, the blood pressure lowering effects of the combination were shown to be additive and in some cases synergistic.

During chronic therapy with Lotrel, the maximum reduction in blood pressure with any given dose is generally achieved after 1-2 weeks. The antihypertensive effects of Lotrel have continued during therapy for at least 1 year. Abrupt withdrawal of Lotrel has not been associated with a rapid increase in blood pressure.

INDICATIONS AND USAGE

Lotrel is indicated for the treatment of hypertension.

This fixed combination drug is not indicated for the initial therapy of hypertension (see DOSAGE AND ADMINISTRATION).

In using Lotrel, consideration should be given to the fact that an ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril does not have a similar risk (see Warnings, Neutropenia/Agranulocytosis).

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks.

CONTRAINDICATIONS

Lotrel is contraindicated in patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Lotrel) may be subject to a variety of adverse reactions, some of them serious. These reactions usually occur after one of the first few doses of the ACE inhibitor, but they sometimes do not appear until after months of therapy.

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotrel should be discontinued and appropriate therapy instituted immediately. *When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3-0.5 mL), should be promptly administered (see ADVERSE REACTIONS).*

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration, and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Hypotension

Lotrel can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Lotrel.

Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering Lotrel as with any other peripheral vasodilator, particularly in patients with severe aortic stenosis.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, Lotrel therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of the benazepril component is increased or a diuretic is added or its dose increased.

If hypotension occurs, the patient should be placed in a supine position, and if necessary, treated with intravenous infusion of physiologic saline. Lotrel treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (incidence probably less than once per 10,000 exposures) but more frequently (incidence possibly as great as once per 1000 exposures) in patients with renal impairment, especially those who also have collagen-vascular diseases such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, Lotrel should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of benazepril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited.

Lotrel has not been adequately studied in pregnant women. When rats received benazepril:amlodipine at doses ranging from 5:2.5 to 50:25 mg/kg/day, dystocia was observed with increasing dose-related incidence at all doses tested. On a mg/m^2 basis, the 2.5 mg/kg/day dose of amlodipine is 3.6 times the amlodipine dose delivered when the maximum recommended dose of Lotrel is given to a 50-kg woman. Similarly, the 5 mg/kg/day dose of benazepril is approximately 2 times the benazepril dose delivered when the maximum recommended dose of Lotrel is given to a 50-kg woman.

No teratogenic effects were seen when benazepril and amlodipine were administered in combination to pregnant rats or rabbits. Rats received dose ratios up to 50:25 mg/kg/day (benazepril:amlodipine) (24 times the maximum recommended human dose on a mg/m^2 basis,

assuming a 50-kg woman). Rabbits received doses of up to 1.5:0.75 (benazepril amlodipine) mg/kg/day; on a mg/m^2 basis, this is 0.97 times the size of a maximum recommended dose of Lotrel given to a 50-kg woman.

Similar results were seen in animal studies involving benazepril alone and amlodipine alone.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: Lotrel should be used with caution in patients with severe renal disease.

When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with **severe congestive heart failure**, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In a small study of hypertensive patients with **unilateral or bilateral renal artery stenosis**, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Lotrel, renal function should be monitored during the first few weeks of therapy.

Some benazepril-treated hypertensive patients with no apparent **preexisting renal vascular disease** have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Dosage reduction of Lotrel may be required. **Evaluation of the hypertensive patient should always include assessment of renal function** (see Dosage and Administration).

Hyperkalemia: In U.S. placebo-controlled trials of Lotrel, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) not present at baseline occurred in approximately 1.5% of hypertensive patients receiving Lotrel. Increases in serum potassium were generally reversible. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes.

Patients With Congestive Heart Failure: Although hemodynamic studies and a controlled trial in patients with NYHA Class II-III heart failure have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Patients With Hepatic Failure: In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. However, since amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Lotrel to patients with severe hepatic impairment (see also WARNINGS).

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Drug Interactions

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotrel. The possibility of hypotensive effects with Lotrel can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotrel.

Potassium Supplements and Potassium-Sparing Diuretics: Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Lotrel and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

Other: Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence of

clinically important adverse interactions.

In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that coadministration with cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin-induced prothrombin response time.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was found when benazepril was given, via dietary administration, to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 18 times (rats) and 9 times (mice) the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria, in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface-area basis), benazepril had no adverse effect on the reproductive performance of male and female rats.

Rats and mice treated with amlodipine in the diet for 2 years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of carcinogenicity. For mice, but not for rats, the highest dose was close to the maximum tolerated dose. On a mg/m² basis, this dose given to mice was approximately equal to the maximum recommended clinical dose. On the same basis, the same dose given to rats was approximately twice the maximum recommended clinical dose.

Mutagenicity studies with amlodipine revealed no drug-related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m² basis, assuming a 50-kg person).

No adverse effects on fertility occurred when the benazepril:amlodipine combination was given orally to rats of either sex at dose ratios up to 15:7.5 mg/kg/day (benazepril:amlodipine), prior to mating and throughout gestation.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters): See Warnings, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers

Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril, so that a newborn child ingesting nothing but breast milk would receive less than 0.1% of the maternal doses of benazepril and benazeprilat.

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while Lotrel is administered.

Geriatric Use

Of the total number of patients who received Lotrel in U.S. clinical studies of Lotrel, 19% were 65 or older while about 2% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Lotrel has been evaluated for safety in over 1600 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 400 were treated for more than 1 year.

The reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 4% of patients treated with Lotrel and in 3% of patients treated with placebo.

The most common reasons for discontinuation of therapy with Lotrel in U.S. studies were cough and edema.*

The side effects considered possibly or probably related to study drug

that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with Lotrel are shown in the table below.

PERCENT INCIDENCE IN U.S. PLACEBO-CONTROLLED TRIALS

	Benazepril/ Amlodipine N=760	Benazepril N=554	Amlodipine N=675	Placebo N=408
Cough	3.3	1.8	0.4	0.2
Headache	2.2	3.8	2.9	5.6
Dizziness	1.3	1.6	2.3	1.5
Edema*	2.1	0.9	5.1	2.2

*Edema refers to all edema, such as dependent edema, angioedema, facial edema.

The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of benazepril resulted in lower incidences as shown in the following table; the protective effect of benazepril was independent of race and (within the range of doses tested) of dose.

PERCENT INCIDENCE BY SEX OF CERTAIN ADVERSE EVENTS

	Benazepril/ Amlodipine		Benazepril		Amlodipine		Placebo	
	Male N=329	Female N=431	Male N=269	Female N=285	Male N=277	Female N=198	Male N=217	Female N=191
Edema	0.6	3.2	0.0	1.8	2.2	9.1	1.4	3.1
Flushing	0.3	0.0	0.0	0.7	0.4	2.0	0.5	0.0
Palpitations	0.3	0.5	0.4	1.4	0.4	2.0	0.5	0.5
Somnolence	0.3	0.0	0.4	0.4	0.4	0.5	0.0	0.0

Other side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials of patients treated with Lotrel or in postmarketing experience were the following:
Angioedema: Includes edema of the lips or face without other manifestations of angioedema (see WARNINGS, Angioedema).
Body as a Whole: Asthenia and fatigue.
CNS: Insomnia, nervousness, anxiety, tremor, and decreased libido.
Dermatologic: Flushing, hot flashes, rash, skin nodule, and dermatitis.
Digestive: Dry mouth, nausea, abdominal pain, constipation, diarrhea, dyspepsia, and esophagitis.
Metabolic and Nutritional: Hypokalemia.
Musculoskeletal: Back pain, musculoskeletal pain, cramps, and muscle cramps.
Respiratory: Pharyngitis.
Urogenital: Sexual problems such as impotence, and polyuria.

Other infrequently reported events were seen in clinical trials (causal relationship unlikely) or in postmarketing experience. These included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, and alopecia.
Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of Lotrel. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine. Other potentially important adverse experiences attributed to other ACE inhibitors and calcium channel blockers include: eosinophilic pneumonitis (ACE inhibitors) and gynecomastia (CCB's).

Clinical Laboratory Test Findings
Serum Electrolytes: See PRECAUTIONS.
Creatinine: Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with Lotrel. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).
Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotrel administration. Elevations of serum bilirubin and uric acid have been reported as have scattered incidents of elevations of liver enzymes.

OVERDOSAGE

Only a few cases of human overdose with amlodipine have been reported. One patient was asymptomatic after a 250-mg ingestion; another, who combined 70 mg of amlodipine with an unknown large quantity of a benzodiazepine, developed refractory shock and died.

Human overdoses with any combination of amlodipine and benazepril have not been reported. In scattered reports of human overdoses with benazepril and other ACE inhibitors, there are no reports of death.

When mice were given single oral doses of benazepril/amlodipine, mortality was 20% at 50:25 mg/kg, 10% at 100:50 mg/kg, and 100% at 500:250 mg/kg. In rats, mortality was 25% (pooling two studies) at 500:250 mg/kg and 100% at 900:450 mg/kg.

Treatment: To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison-Control Center. Telephone numbers of certified poison-control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibilities of multiple-drug overdoses, drug-drug interactions, and unusual drug kinetics in your patient.

The most likely effect of overdose with Lotrel is vasodilation, with consequent hypotension and tachycardia. Simple repletion of central fluid volume (Trendelenburg positioning, infusion of crystalloids) may be sufficient therapy, but pressor agents (norepinephrine or high-dose dopamine) may be required. Overdoses of other dihydropyridine calcium channel blockers are reported to have been treated with calcium chloride and glucagon, but evidence of a dose-response relation has not been seen, and these interventions must be regarded as unproven. With abrupt return of peripheral vascular tone, overdoses of other dihydropyridine calcium channel blockers have sometimes progressed to pulmonary edema, and patients must be monitored for this complication.

Analyses of bodily fluids for concentrations of amlodipine, benazepril, or their metabolites are not widely available. Such analyses are, in any event, not known to be of value in therapy or prognosis.

No data are available to suggest physiologic maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of amlodipine, benazepril, or their metabolites. Benazeprilat is only slightly dialyzable; attempted clearance of amlodipine by hemodialysis or hemoperfusion has not been reported, but amlodipine's high protein binding makes it unlikely that these interventions will be of value.

Angiotensin II could presumably serve as a specific antagonist-antidote to benazepril, but angiotensin II is essentially unavailable outside of scattered research laboratories.

DOSAGE AND ADMINISTRATION

Amlodipine is an effective treatment of hypertension in once-daily doses of 2.5-10 mg while benazepril is effective in doses of 10-80 mg. In clinical trials of amlodipine/benazepril combination therapy using amlodipine doses of 2.5-5 mg and benazepril doses of 10-20 mg, the antihypertensive effects increased with increasing dose of amlodipine in all patient groups, and the effects increased with increasing dose of benazepril in nonblack groups. All patient groups benefited from the reduction in amlodipine-induced edema (see below).

The hazards (see WARNINGS) of benazepril are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much more common than the latter. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced. Therapy with any combination of amlodipine and benazepril will thus be associated with both sets of dose-independent hazards, but the incidence of edema will generally be less than that seen with similar (or higher) doses of amlodipine monotherapy.

Rarely, the dose-independent hazards of benazepril are serious. To minimize dose-independent hazards, it is usually appropriate to begin therapy with Lotrel only after a patient has either (a) failed to achieve the desired antihypertensive effect with one or the other monotherapy, or (b) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing edema.

Dose Titration Guided by Clinical Effect: A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine) alone or with benazepril (or another ACE inhibitor) alone may be switched to combination therapy with Lotrel. The addition of benazepril to a regimen of amlodipine should not be expected to provide additional antihypertensive effect in African-Americans. However, all patient groups benefit from the reduction in amlodipine-induced edema. Dosage must be guided by clinical response; steady-state levels of benazepril and

amlodipine will be reached after approximately 2 and 7 days of dosing, respectively.

In patients whose blood pressures are adequately controlled with amlodipine but who experience unacceptable edema, combination therapy may achieve similar (or better) blood-pressure control without edema. Especially in nonblacks, it may be prudent to minimize the risk of excessive response by reducing the dose of amlodipine as benazepril is added to the regimen.

Replacement Therapy: For convenience, patients receiving amlodipine and benazepril from separate tablets may instead wish to receive capsules of Lotrel containing the same component doses.

Use in Patients With Metabolic Impairments: Regimens of therapy with Lotrel need not take account of renal function as long as the patient's creatinine clearance is >30 mL/min/1.73m^2 (serum creatinine roughly ≤3 mg/dL or 265 µmol/L). In patients with more severe renal impairment, the recommended initial dose of benazepril is 5 mg. Lotrel is not recommended in these patients.

In small, elderly, frail, or hepatically impaired patients, the recommended initial dose of amlodipine, as monotherapy or as a component of combination therapy, is 2.5 mg.

HOW SUPPLIED

Lotrel is available as capsules containing amlodipine/benazepril HCl 2.5/10 mg, 5/10 mg, and 5/20 mg. All three strengths are packaged with a desiccant in bottles of 100 capsules.

Capsules are imprinted with "Lotrel" and a portion of the NDC code.

Dose	Capsule Color	NDC Code Bottle of 100
2.5/10 mg	white capsule with 2 gold bands	NDC 0083-2255-30
5/10 mg	light brown capsule with 2 white bands	NDC 0083-2260-30
5/20 mg	pink capsule with 2 white bands	NDC 0083-2265-30

Storage: Do not store above 86°F (30°C). Protect from moisture and light.

Dispense in tight, light-resistant container (USP).

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